U.S. Measurement System

NIST National Institute of Standards and Technology

Final Agenda

Imaging as a Biomarker: Standards for Change Measurements in Therapy

A U.S. Measurement System Workshop

September 14-15, 2006
National Institute of Standards and Technology
Administration Building – Red Auditorium

Closing Session

Michael W. Vannier, MD
Moderator

Closing Session Summary

- Priorities and Next Steps for the agencies and the stakeholders after participating in the workshop.

- Keeping in mind that the agencies have to carry back to their decision makers

  – “Why industry can't do it alone?

  … or …

  – Why that won't produce the best result for the nation?“

  ... and for NIST …

  – “Why NIH and FDA can't do it alone" ...

Presentation Outline

- Statement of the Problem
- Criteria for Success
- Stakeholders
- Potential Solutions
- Roles
  - Industry
  - Professional Societies
  - Government
  - Academia

Imaging as a biomarker

- Who is involved?
  - Government agencies (NIH, FDA, NIST)
  - Industry (Medical imaging & Pharmaceuticals)
  - Professional Societies (RSNA, ACR, ISMRM, SPIE, AAPM)
  - Industry Associations (NEMA, PhRMA)

Imaging as a biomarker

- **Biomarkers are biological indicators of disease or therapeutic effects** that can be measured by *in vivo* biomedical imaging and molecular imaging in particular, as well as other *in vitro* or laboratory methods.

- Recent work has shown that biomedical imaging can provide an ***early indication of drug response*** by use of X-ray, MRI, CT or PET-CT.

Imaging as a biomarker

VARIABILITY

- Many **sources of uncertainty** exist in imaging as a biomarker.
- **Biological variability**, for example, is a factor that is both drug- and patient-dependent and thus difficult to characterize or model.
- Additional uncertainties are associated with the image **data collection** platform and the robustness of **software tools** used for:
  - quantitative measurement of change over time
    - tumor volume
    - radioactive tracer activity
    - contrast agent dynamics
- All these sources of uncertainty significantly affect the **statistical power of clinical drug or therapy trials**.

IHE Lessons

- Industry should drive the process
- A neutral party should act as a facilitator
- Publicity is key to maintain momentum and to draw in new participants

Dr. Jost

PhRMA's Perspective

- Need for consensus and partnership toward developing industry standard, regulatory and clinical guidelines for harmonizing and standardizing imaging in clinical trials to manage quality, cost and time.

Dr. Analoui

Content of Standards

- Data collection
- Image post-processing
- Data management and archiving
- Quality control

Four Key Questions

- Why do we need standards? (impact on quality, cost, speed)
- When do we need standardization vs. harmonization?
- Priority list of areas that guidelines are required: Limited, initial list of modality-disease-endpoint specific projects that are most critical for key players to begin with.
- Identify key partners and expected role for each of them. Partners and their roles could be project specific.

Results of Breakout Sessions

The Rise and Fall of CORBA

CORBA is the acronym for **C**ommon **O**bject **R**equest **B**roker **A**rchitecture

Depending on exactly when one starts counting, CORBA is about 10-15 years old. During its lifetime, CORBA has moved from being a bleeding-edge technology for early adopters, to being a popular middleware, to being a niche technology that exists in relative obscurity. It is instructive to examine why CORBA—despite once being heralded as the "next-generation technology for e-commerce"—suffered this fate. CORBA's history is one that the computing industry has seen many times, and it seems likely that current middleware efforts, specifically Web services, will reenact a similar history.

Michi Henning, ZeroC
ACM QUEUE, JUNE 2006, VOL. 4 NO. 5

AAPM Perspective

- Need exists for an “Imaging Physics Center”
- Integrate planning images; treatment plans; verification images, … and submit them digitally.
- Quality control of treatment planning and delivery.
- Radiation therapy is increasingly dependent on imaging data

SNM Perspective

- Molecular imaging
- Radiopharmaceutical GMP/GCP for PET tracers
- Quantitative tracer uptake determination (SUV and successors)
- Phantom testing – multicenter imaging system performance trial
- Empanelled a group of experts in “clinical trials”

The Opportunity

- Whether it's Alzheimer's disease, osteoarthritis, lung cancer or many other potentially treatable conditions, multicenter clinical trials are required to test hypotheses (and answer regulatory questions).
- Imaging promises to provide surrogate endpoints (e.g., biomarkers) that predict clinical outcomes.
- Imaging results can be used to decide whether a treatment is working or not, long before clinical outcome can be determined.
- Imaging biomarkers could facilitate decision making thereby ***reducing time and lowering cost***
  - so new treatments can benefit patients sooner

Importance of the Problem

- Medical images are frequently acquired and evaluated in clinical trials of drugs and devices
- Lack of standardization (for collecting and managing images) increases cost and introduces avoidable delay

Why don’t we do this already?

- The **variability** inherent in these multicenter trials that use imaging is too high.
- **Standards** developed for clinical medicine (care of individual patients) are insufficient to pool data from multiple sites (different instruments, locally varied acquisition protocols, …)
- **Sharing of data** in clinical trials is rare
  - Sharing is the exception, rather than the rule.
- HIPAA is an impediment (need for de-identification)
- Processes to distribute, update, track clinical trial & image data are absent in most hospitals and clinics. (We have this infrastructure for clinical needs within healthcare organizations, but external interfaces are undeveloped).

Imaging biomarkers

- Must have comprehensive databases (images, clinical data & outcomes) to develop and validate biomarkers
- The design and construction of databases can be independent from the synthesis of biomarkers (e.g., tools to compute them)
- Exact details of the biomarker(s) need not be defined when the database is assembled.
- Validation is essential (validity of marker itself, as well as validity of software tools and integrity of databases)

Analogy to Serology

- Banked specimens (serum from blood samples) are routinely collected and stored in biobanks.
- Specimens may be linked with clinical records (including outcomes).
- Biomarker developer obtains access to specimens and receives a small amount of each sample.
- These are tested, and the predicted results compared with known outcomes.
- Test set **vs.** Training set (for pattern recognition)

Quality Criteria

- Cross-site consistency
- Known sources of variation
- Reader evaluation
  - Independent readers must work across platforms (e.g., GE, Siemens, Philips, ….)
- Documentation (imaging manuals) that match the requirements
- Site monitoring – phantom / calibration
- Archive – integrity; completeness; retention of records
- Document all deviations

Dr. George Mills

Medical Imaging

- Overwhelming majority of images are gathered to answer clinical questions that pertain to management of individual patients.
  - Incredible variability; The “Wild West”
- Specialized exams are done for clinical trials, where the questions pertain to groups rather than individual patients.
  - Reduced variation in a single center study, where investigator can control most sources
- Multicenter clinical trials are a special case, where harmonization across sites is needed so pooling of data can be done.

Medical Imaging and FDA

- The standards for acceptable variation, need for auditable records keeping, and linkage to ancillary clinical data are more demanding than ordinary medical practice.
- Medical imaging systems, PACS, workstations, and interfaces **are NOT designed** to support this activity.
- Reliable decision making based on medical imaging requires comprehensive standards (that fill gaps) and tools to maintain integrity and ensure quality of results.

Dr. George Mills

Need to Share

- Data sharing in clinical applications is an unwelcome burden to original investigators
- Infrastructure to do this is costly and complex (and largely non-existent)
- Reasons for not sharing are numerous

Precedents

- **ADNI** provides de-identified MRI, PET and clinical data for 54 sites, 450 subjects.
  - ADNI-info.org has this information…
- **OAI** provides 3T MRI data of joints.
- **ACRIN** and **RIDER** have image databases
- **ATC** has managed digital data for image-guided radiotherapy, including Phase 3 clinical trials
  - ATC is a model for image-guided therapy planning & evaluation multicenter trials

Dr. Weiner & Dr. Purdy

Why not do this alone?

- Medical imaging is huge and complex.
- New standards imply a change of direction.
- Key constituents are independent and powerful
  - e.g., clinical healthcare enterprise, medical imaging industry, FDA, …
- There are few models of successful collaboration among all of these entities.

Stakeholders

- Sponsor (Pharmaceutical Mfgr.)
- CRO
- Clinical sites
- Patients

- Government
- Medical Imaging Industry
- Professional Societies; Academia

Why doesn’t the medical imaging industry do this already?

- Customers don’t ask for it.
- No one pays for it.
- Most clinicians wouldn’t use it.
- No specific competitive advantage.
  - In fact, the variation in systems is used for competitive advantage.
- Regulatory overview of products is a major cost and may increase time to market.
- Liability concerns.

- **Imaging in multicenter clinical trials**

REQUIRES

- **Standardization of multicenter imaging**

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“Precision is the goal of multi-center imaging”

- Implement the saqme, detailed imaging acquisition protocols at all clincial sites
- Clinical trial imaging = “established” NOT “cutting-edge”
- Ooptimize image processing & reconstruction software
  - Avoid manual techniques
  - Select and develop semi-automated or automated

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Criteria for Success

- Emergence and implementation of consensus multi-center imaging standards
- FDA uses Independent Review Charters (IRC): clinical protocol, statistical analytical plan

  2000 =2; 2003 =<12; 2006 (to date) = >36

  * Prospectively designed, reviewed and approved by FDA prior to the initiation of Phase 3 studies

Dr. George Mills

Model: Imaging Biomarkers used in planning and evaluating therapy

- ATC = Advanced Technology Consortium
- Radiotherapy multicenter clinical trials
  - Planning is based on images
  - Therapy is delivered under image control
  - Response is measured with images
- Large Phase 3 clinical trials have been conducted and results reported
  - All data is in a digital repository
  - 2° analyses have been performed

Dr. Purdy

IBM Perspective

- “Information-based medicine”
- Integrate diverse information, including images
- IBM Imaging Biomarker Summit meetings (Dec 2005, June 2006)
- JANUS data model for future drug submissions

Dr. Hehenberger

Imaging CRO Perspective

- Academic vs. Commercial trials
  - Lowest common demoninator
  - Strict regulatory oversight
  - Strict software validation reqruiement
- Dozens vs. hundreds of trials; thousands of sites (including community centers)
- Investigators are clinicians (not radiologists)
- Numerous standardization opportunities (trial design, site equipment, acquisition, transfer of images, independent reads, response criteria and change detection, tools, QC, submission, compliance and certification, archival storage and re-use, audit trails (IHE).
- What about international clinical trials?
- Media transfer and legacy infrastructure is solved problem.
- Network transfer infrastructure is challenging.
- IHE Clinical Trial Profile – Deidentification for teaching files is similar to clinical trials

Software

- Tools are poorly supported in academic world
- Most academic software is not reusable
- caBIG eXtensible Imaging Platform (XIP) effort (standards-based)
  - Uses standards-based open architecture system for oncology
  - Very comprehensive: genetic data, clinical data, images, the kitchen sink (and the plumbing)….

Clinical Trial Audit Trails

- 21 CFR 11 requirement for records
  - Required by FDA
  - Standard for electronic recordkeeping
  - NOT part of current clinical care delivery systems (PACS, RIS, HIS)

- Standards are needed if they add value & will be used (globally)

Next Steps

- What should Pharma do?
- What should Professional Societies do?
- What should Medical Imaging System Manufacturers do?
- What should Government do?
- What should Academia do?

What should Pharma do?

- Seize the initiative; Take the lead…
- State the problem
  - e.g., Review and refine the problem statement
  - Engage FDA early
- Set priorities
- Provide resources
- Link CDISC to DICOM
- Monitor progress; Test FDA’s response

What should Professional Societies do?

- Recognize and endorse “Imaging Biomarkers”
- Publicize the issue to their membership
- Empanel domain experts that do clinical trials and engage them with Pharma & Govt
- Act as facilitator
- Define “quality” of clinical trials in their domain; Define and disseminate best practices for clinical trials in their domain; Case studies with critique
- More publicity

What should Medical Imaging Systems Manufacturers do?

- Respond to “imaging biomarkers” initiative
- Attend and participate in “DICOM” meetings that address “imaging biomarkers” needs
- Link DICOM to CDISC
- Educate their users
- Recognize the advantage of imaging clinical trials in the long term future success of their products…
- Cross licensing of software technology

What should Government do?

- Ensure inter-agency communication and collaboration (No one agency can do this alone)
- NIST can define the problem and distill the essential needs so “lack of standardization” can be approached; provide a framework (IT)
- Whitepaper on “Imaging Biomarkers”
- Sponsor testbeds; support “Imaging Physics - Quality Center” = use the experience of RT / ATC / RTOG in image-guided therapy trials as model
- Monitor progress and publicize progress
- Facilitate data sharing = sponsor open archive
- Develop standard phantoms (e.g., for brain MRI)

What can Academia do?

- Include “clinical trials” infrastructure needs in procurement of new systems (imaging scanners, PACS, …)
- Integrate clinical trials records with images (and genomic data) in single center studies
- Share their results and recognize sharing as important (rather than exception or an option)
- Engage Radiologists / Medical Physicists / Nuclear Medicine Physicians / MRI experts in the design of new trials
- Enhance the role of clinician-scientists with imaging expertise that do human oriented research

Overall Summary

- There is a critical and immediate need to establish and implement standards for medical imaging in clinical trials
- On completion, a standardization initiative would benefit patients by providing new drugs and devices to treat their condition.
- Other beneficiaries include industry, government, payors, and the public.

Panel Discussion

Based on the discussions you heard at the workshop and breakouts:

- 1) What should be the **Next Steps** for imaging standards and measurement needs?
- 2) What are the **stakeholder roles** and **near-term priorities** for imaging standards and measurement needs?
- 3) **What "push" is needed** by everyone to get players together to address standards and measurement problems that are too large for any one sector, agency or group to resolve?

Cross Licensing

- MRI system requires 1500 patents, approximately equally distributed among the major manufacturers
- 5 year agreements allow use of technology